Model-based Insulin Sensitivity and Pharmacodynamic (PD) Surfaces

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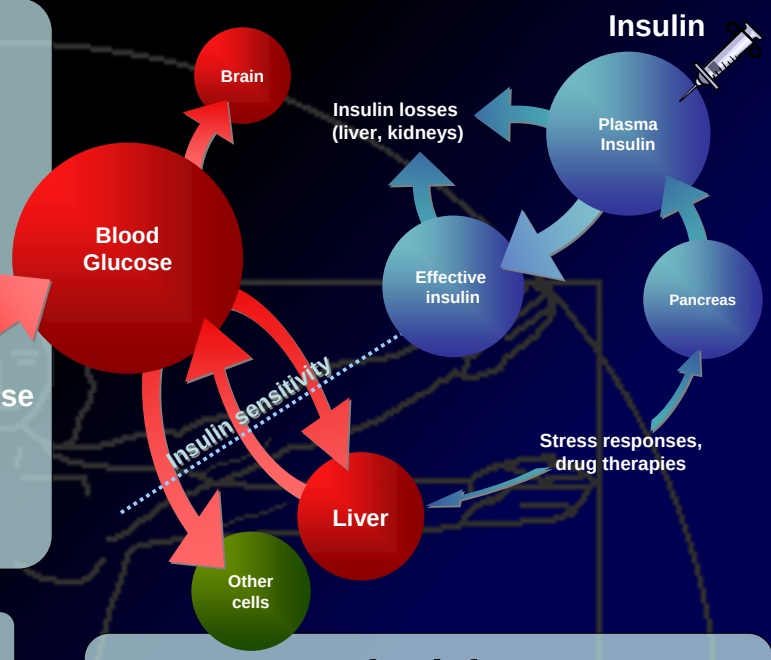
Background and Aims

The main methods for determining insulin sensitivity with high resolution are either clinical (hyperinsulinemic eu- or hyper- glycemic clamp) or model-based (e.g. FSIVGTT). Typically, the model-based methods use some form of the Minimal Model (MM), which has been shown to underestimate insulin sensitivity in some cases.

This research presents a method of analysing a model's PD surface to determine:

- If its fundamental dynamics capture clinical behaviours
- What, if any, dynamics are missing from a model
- What, if any, dynamics are not necessary

There is currently no fixed method for doing such an analysis and most models are validated on the ability to fit time trajectories of patient-specific clinical data. This approach tests the ability of a model to capture data and trends (in steady state) across an entire PD surface.



	Value
P_G	0.006 min^{-1}
V_G	13.3 L (for 70kg), V_G = 0.19*Mass (kg)
P_{end}	1.2 mmol/L/min (0 for the MM case)
S_I	1.5e-3 – 3.5e-3 L/mU/min
α_G	1/20 – 1/80 L/mU (0 for the MM case)
α_{G2}	1/5 – 1/20 L/mmol (0 for the MM case)

ND1, 2 and MM: $\dot{G} = -p_G G - S_I \frac{G}{1+\alpha_{G2}G}\frac{Q}{1+\alpha_G Q} + \frac{P(t)}{V_G} + \frac{P_{end}}{V_G}$

RM:

EndoBal = Hepatic – Renal – P13 – P14

Hepatic = -0.46min^{-1} G – 1.475mmol/min/mU I_s + 1.259mmol/L/min; G_{max}=12.0 mmol/L

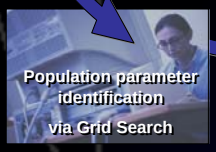
Renal = 0.004L/mmol/min G^2 – 0.064min^{-1} G + 0.278mmol/L/min

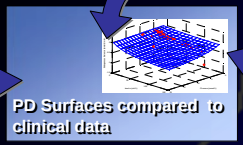
P13 = 0.56min^{-1} *G/(G + 1.5mmol/L)

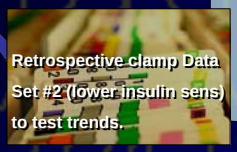
P14 = 5.09mmol/L/min/mU G*I_s/(G+5.0 mmol/L)

$I_s = I * 1/((I\text{-}0.083\text{mU/L})^{1.77} + (0.539\text{mU/L})^{1.77})^{(1/1.77)}$

System models







Methodology

Four clinically validated models are analysed:

- Minimal Model (MM)
- A Receptor Model (RM) from Arleth et al (2000)
- Two non-linear dynamic models (ND1 and ND2)

Two sets of euglycemic and hyperglycemic clamp data are used:

- **Data Set #1:** Eu- and hyper- glycemic clamps are used to find a set of population parameters for each model (N=77)
- **Data Set #2:** Euglycemic clamp data from a lower insulin sensitivity cohort (N = 146) are used to see if the fitted models from step #1 can fit by just shifting the insulin sensitivity parameter (A model validation test)

Results and Conclusions

Performance Metrics:

- RMS Error (RMS)
- Absolute Mode of Error (AME)
- Frequency of Error Near Zero (FNZ)

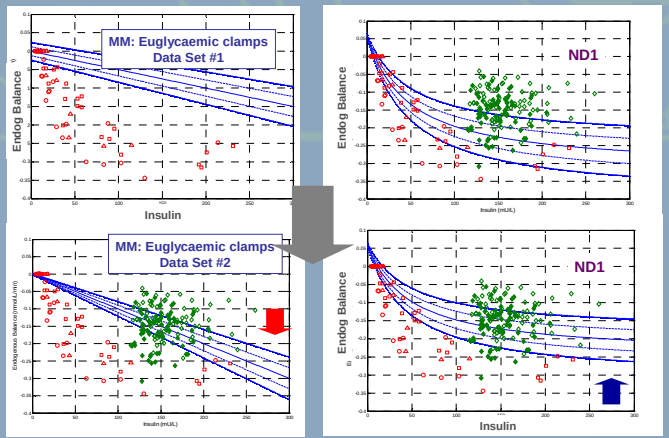
Data Set #1 Results:

Model	Values
ND1	α_G = 1/47 L/mU, α_{G2} = 0 L/mmol, S_I = 0.0016 L/mU/min RMS = 0.07; AME = -0.01, FNZ = 36
ND2 Best FNZ	α_G = 1/47 L/mU, α_{G2} =1/6 L/mmol, S_I = 0.0029 L/mU/min RMS = 0.05; AME = -0.01, FNZ = 39
ND2 Best RMS	α_G = 1/50 L/mU, α_{G2} =1/6 L/mmol, S_I = 0.0032 L/mU/min RMS = 0.05; AME = -0.00, FNZ = 38
MM	α_G = α_{G2} = 0 L/mU & L/mmol S_I = 0.0001 L/mU/min RMS = 0.29; AME = -0.05, FNZ = 24
RM	RMS = 0.04; AME = -0.01, FNZ = 32

Note: MM slope high for Data Set #1 to reduce the error for hyperglycemic clamp results not shown here, thus reducing total error

Data Set #2 Results: Scaling Insulin Sensitivity

	RMS	FNZ (of 146)	Scaled S_I	Prior S_I	α_{G1}	α_{G2}
MM	0.56	12	2.0e-4	1.0e-4	0	0
ND1	0.05	54	1.3e-3	1.6e-3	1/47	0
ND2	0.05	60	2.3e-3	3.1e-3	1/47	1/6
RM	0.05	61	0.40	1.0	1.77th power or ~1/50	1/5



- MM under predicts insulin sensitivity. MM at low insulin sensitivity provides the wrong trend result. These match reported results.
- Saturation dynamics play an important role in providing good fits across PD surface.
- Trend prediction is also reliant on the use of (at least) effective insulin saturation, which the MM does not have.
- Approach can complement typical fitting and prediction validation methods and provide information on which dynamics are necessary or sufficient in any similar model.

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